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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN - 1 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Assure (Quizalafop p-ethyl; D-NC 302): Review of supplemental data for a mouse lymphoma assay for forward mutation

Caswell No. 215D **DP Barcode:** D211878
EPA ID No. 000352-00541 **Submission No.** S481405
PC Code: 128711

TO: V. Waters / R. Taylor, PM Team 25
Registration Division (7505C)

FROM: Whang Phang, Ph.D. 5/25/95
Pharmacologist
Tox. Branch II/HED (5709C)

THROUGH: James Rowe, Ph.D. James N. Rowe 5/25/95
Section Head
and
Marcia van Gemert, Ph.D. Marcia van Gemert 5/31/95
Branch Chief
Tox. Branch II/HED (7509C)

The registrant, E.I. dupont de Nemours & Co., Inc., submitted a set of supplemental data to provide historical data from IITRI for the gene mutation in cultured mammalian cells. This set of data has been reviewed, and the Data Evaluation Report (DER) is attached. The citation of the study and the conclusion of this review are presented below:

Ketels, K.V. (1991) Mouse lymphoma assay for forward mutation on D-NC320. Unpublished study conducted by IIT Research Institute. Study No. 18. June 1991. Submitted to the EPA by E.I. duPont de Nemours & Co.; EPA MRID No. 41936601.

Previous reviewers of this study considered this study to be **unacceptable** because of the high back ground mutation frequencies for solvent control, dimethyl sulfoxide, both in the absence and presence of S9 activation. The high back ground mutation may have limited the ability of the test system to detect a weak positive response.

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Based on the re-evaluation of the supplemental data and additional information indicating that neither the resolved D+ isomer nor the racemic mixture (1:1 ratio of the D+ and L- isomer) were positive in genetic toxicology batteries, additional useful information may not be gained by repeating the mouse lymphoma assay. The study is, therefore, upgraded and reclassified as acceptable.

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ASSURE **MAMMALIAN CELLS IN CULTURE GENE MUTATION**

EPA Reviewer: Nancy E. McCarroll
Review Section III,
Toxicology Branch II/HED 7509C
EPA Section Head: James N. Rowe, Ph.D.
Review Section III,
Toxicology Branch II/HED 7509C

Signature: Nancy E. McCarroll
Date: 5/10/95
Signature: James N. Rowe
Date: 5/15/95

DATA EVALUATION REPORT

STUDY TYPE: Gene mutation in cultured mammalian cells (mouse lymphoma cells)

DP BARCODE: D211878

SUBMISSION NO: S481405

P.C. CODE: 128711

MRID NUMBER(S): 434737-00,-01

TEST MATERIAL: D-NC302 Technical

SYNONYM(S): Assure; Quizalafop p-ethyl

STUDY NUMBER: LO8157

SPONSOR: Nissan Chemical Industries, Ltd., Tokyo, Japan / DuPont Agricultural Products, Wilmington, DE

TESTING FACILITY: IIT Research Institute, Chicago, IL

TITLE OF REPORT: Supplement No.1 to: Mouse Lymphoma Assay for Forward Mutation of D-NC302

AUTHOR(S): K.V. Ketels (IIT Research Institute); M.M. Chubb (DuPont Agricultural Products)

REPORT ISSUED: December 1, 1994

CONCLUSIONS--EXECUTIVE SUMMARY: Comments were received from the sponsor (MRID Nos. 434737-00,-01) regarding the EPA toxicology review, completed October 23, 1992, of a mouse lymphoma forward gene mutation assay conducted with D-NC302 technical[1].

EPA reviewers considered the study unacceptable because of concerns that the high background mutation frequencies (MFs) for the solvent control, dimethyl sulfoxide (DMSO) both in the absence and presence of S9 activation may have limited the ability of the test system to detect a weak positive response.

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[1]Ketels, K.V. Mouse Lymphoma Assay for Forward Mutation of D-NC 302 (Unpublished Study No. 18; prepared by IIT Research Institute, Chicago, Il and submitted by Nissan Chemical Industries, Ltd., Tokyo, Japan; dated June 1991) MRID No. 419366-01.

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Based on a reevaluation of the data and in consideration of the additional information indicating that neither the resolved D+ isomer nor the racemic mixture (1:1 ratio of the D+ and L-isomer) were positive in genetic toxicology batteries, we conclude that nothing further would be gained by repeating the mouse lymphoma assay. The study is, therefore, upgraded and reclassified as acceptable. By analogy to the above formulations of Assure, D-NC302 is considered negative for the induction of gene mutations in the mouse lymphoma assay. Our detailed rationale for upgrading the study is presented below:

A. RESPONSE TO COMMENTS:

1. High Background Frequency for Mouse Lymphoma Cells: Neither the sponsor's representative nor the author of the original study report disputed the Agency's assessment that the high background frequency for the solvent control, dimethyl sulfoxide (DMSO) both in the absence (MF = 204×10^{-6}) and presence (MF = 137×10^{-6}) of S9 activation compromised the ability of the test system to detect a potential weak mutagenic effect. Similarly, the historical data provided by the performing laboratory did not alter this assessment.

2. Need for Additional Studies: The larger issue arising from the insensitivity of the mouse lymphoma assay conducted with D-NC302 relates to whether the study should be repeated. The sponsor contends that additional studies are not necessary because both the resolved D+ isomer and the racemic mixture (1:1 ratio of the D+ and L-isomer) were negative in the following genetic toxicology tests:

NC-302	MRID No.	Result
Ames test	000128205	-
CHO gene mutation	000128204	-
In vitro chromosome aberrations in CHO	--	-
UDS in rat hepatocytes	000128202	-
Micronucleus	000128203	-
D+ Isomer		
Ames test	41206108	-
Mouse lymphoma	41206109	-
UDS in rat hepatocytes	41206110	-

Note: The MRID No. listed by the sponsor for the UDS assay with the D+ isomer was incorrect; the error was corrected by our reviewers.

We agree with the sponsor's argument. Since there was no evidence of a mutagenic effect in the flawed study, the negative findings with the racemate mixture and the D+ isomer support the conclusion that nothing further would be gained by repeating the mouse lymphoma assay with D-NC302.

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B. APPENDIX ATTACHED: Reference letter M.M. Chubb (DuPont) to R.J. Taylor (USEPA), dated December 1, 1994. Supplement No.1 to : Mouse Lymphoma Assay for Forward Mutation of D-NC302 (revised) LO8157 K.V. Ketels

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END